

Pharmacokinetics (PK) of Once Daily versus Twice Daily Lamivudine and Abacavir in HIV-1 Infected Children- PENTA 13

Anna Bergshoeff ^(1,2), David Burger ^(1,2), Corrie Verweij ^(1,2), Laura Farrelly ⁽³⁾, Jacquie Flynn ⁽⁴⁾, Marthe LeProvost ⁽⁵⁾, Sarah Walker ⁽³⁾, Vito Novelli ⁽⁴⁾, Hermione Lyall ⁽⁵⁾ and Diana Gibb ⁽³⁾, on behalf of the Penta-13 study group.

(1) University Medical Centre Nijmegen, The Netherlands, (2) Nijmegen University Center for Infectious diseases (NUCI), The Netherlands, (3) MRC Clinical Trials Unit, London, United Kingdom, (4) Infectious Diseases Unit, ABC Family Clinic, Great Ormond Street Hospital for Sick Children, London, United Kingdom, (5) Infectious Diseases Unit, Family Clinic, St. Mary's Hospital, London, United Kingdom

Acknowledgements: children and their caretakers are acknowledged for participation in this study. Lynda Harper and Debbie Johnson are acknowledged for their assistance. Khalid Asouit, Michel Broekman and Carlo Rajmakers are acknowledged for processing and analysis of the plasma samples. This study was financially supported by Glaxo Smithkline, United Kingdom.



Poster 934
Abstract S-34

11th Conference of Retroviruses and Opportunistic Infections, Feb 8-11, 2004

Introduction

- Simplification of antiretroviral therapy by reducing dosing frequency can enhance compliance to medication in both HIV-1 infected adults and children.
- Venkatesh is known on once daily (q24h) use of nucleoside analogues in HIV-1 infected children.

Objectives

1. To compare the plasma pharmacokinetics (PK) of lamivudine (3TC) 8 mg/kg q24h with 4 mg/kg q12h and of abacavir (ABC) 16 mg/kg q24h with 8 mg/kg q12h.
2. To evaluate age-related differences in the PK of these agents.

Methods

Study design

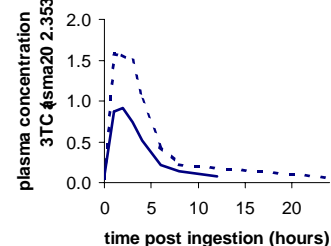
- Open label, single sequence, two-period cross-over study
- Children were enrolled 1:1 into age strata of ≥ 2 - <6 and >6 - <13 years old
- Intravenous plasma PK sampling was performed at steady-state during use of 3TC and/or ABC q12h and 4 weeks after switch to q24h
- Plasma concentrations of 3TC and ABC were determined by a validated method of HPLC.
- Non-compartmental PKs were applied. Geometric mean ratios (GMR) with 90% confidence intervals (CI) of PK parameters were calculated to compare q24h and q12h regimens.
- HIV-1 RNA load measurements were performed at baseline and routinely during the follow-up
- Reported are PK data and a summary of safety and virologic efficacy data up to week 12.

Inclusion criteria

- age ≥ 13 years and confirmed HIV-1 infection
- using combination treatment containing 3TC 4 mg/kg q12h and/or ABC 8 mg/kg q12h; willing to switch 3TC and/or ABC to q24h use
- clinically stable:
 - HIV-1 RNA load suppressed, or non-suppressed but relatively low (400-20,000 copies/mL)
 - CD4 cell count stable or rising prior to study entry
- children and/or parents able to give informed consent

Exclusion criteria

- Intercurrent illness; grade 3 or higher renal or liver function abnormalities
- Other than antiretroviral medication (except *Pneumocystis Carinii* Pneumonia Prophylaxis)



| Pharmacokinetic parameter 3TC | 4 mg/kg q12h (GM (90% CI)) (N=19) | 8 mg/kg q24h (GM (90% CI)) (N=19) | Within-patient comparison q24h vs. q12h (GMR (90% CI)) (N=19) |
|-------------------------------|-----------------------------------|-----------------------------------|---|
| AUC ₀₋₂₄ (mg/L*h) | 8.88 (7.67-10.28) | 9.80 (8.64-11.12) | 1.12 (1.03-1.21) |
| C _{max} (mg/L) | 1.11 (0.96-1.29) | 2.09 (1.80-2.42) | 1.90 (1.67-2.16) |
| C _{min} (mg/L) | 0.067 (<0.050-0.153) | 0.050 (<0.050-0.076) | N.A.* |
| (median (range)) | | | |
| Cl/F*kg (L/h*kg) | 0.90 (0.78-1.04) | 0.80 (0.70-0.92) | 0.89 (0.82-0.96) |

* not available

Table 3: PK parameters of ABC 8 mg/kg q12h and 16 mg/kg q24h and within-patient comparison of q24h vs. q12h

| Pharmacokinetic parameter ABC | 8 mg/kg q12h (GM (90% CI)) (N=14) | 16 mg/kg q24h (GM (90% CI)) (N=14) | Within-patient comparison q24h vs. q12h (GMR (90% CI)) (N=14) |
|-------------------------------|-----------------------------------|------------------------------------|---|
| AUC ₀₋₂₄ (mg/L*h) | 9.91 (8.26-11.89) | 13.37 (11.80-15.16) | 1.35 (1.19-1.54) |
| C _{max} (mg/L) | 2.14 (1.79-2.56) | 4.80 (4.04-5.71) | 2.25 (1.83-2.77) |
| C _{min} (mg/L) | 0.025 (<0.015-0.070) | <0.015 (<0.015-0.046) | N.A.* |
| (median (range)) | | | |
| Cl/F*kg (L/h*kg) | 1.58 (1.30-1.93) | 1.16 (1.01-1.34) | 0.73 (0.64-0.84) |

*: not available

Results

Baseline

- 24 HIV-1 infected children using antiretroviral combination therapy were enrolled; median age (range) 5.6 (2.1-12.8) years; median body weight (range) (22.5 (12.5-60.5) kg
- 20/24 children (10 girls/10 boys) had complete PK data of 3TC (N=19) and/or ABC (N=14)
- One child used amoxicillin/clavulanic acid on the day of PK sampling. Data of this child were not excluded since no interference of the drug with the PK of 3TC nor ABC is expected.
- At baseline, in 16/20 (80%) children, plasma HIV-1 RNA load was <100 copies/mL.

PK of 3TC (Tables 1 and 2)

- The GMR of AUC₀₋₂₄ q24h vs. q12h significantly exceeded 1.0, suggesting non-inferiority in terms of PK of the q24h regimen.
- For C_{max} q24h vs. q12h, GMR approximated 2, suggesting linear pharmacokinetics of 3TC.
- Cl/F*kg was significantly lower for q24h than q12h 3TC.
- No significant differences were found with respect to GMRs between children ≥ 2 -6 years and children >6 - <13 years old: GMRs were 1.17 and 1.06 for AUC₀₋₂₄, 1.84 vs. 1.96 for C_{max} and 0.85 vs. 0.93 for Cl/F*kg, respectively (p values all >0.30, data not shown).
- Children ≥ 2 -6 years old tended to have lower plasma levels of 3TC than children >6 - <13 years old; this difference was most evident for C_{min} (Table 2).

PK of ABC (Tables 3 and 4)

- The GMR of AUC₀₋₂₄ of the q24h vs. q12h regimen of ABC significantly exceeded 1.0, suggesting non-inferiority in terms of PK of the q24h with regard to q12h regimen.
- For C_{max} of q24h vs. q12h regimen, GMR exceeded 2, possibly reflecting more than dose-proportional pharmacokinetics of ABC.
- Cl/F*kg was significantly lower for q24h versus q12h ABC.
- No difference was found between GMRs in children ≥ 2 -6 years and children >6 - <13 years old: GMRs were 1.46 and 1.17 for AUC₀₋₂₄, 2.61 versus 1.72 for C_{max} and 0.67 versus 0.85 for Cl/F*kg, respectively (p values all >0.08, data not shown).
- No significant differences in AUC₀₋₂₄, C_{max} and Cl/F*kg of ABC were observed between children ≥ 2 -6 years old and children >6 - <13 years old (Table 4).
- However, in the younger age group, all 9 children using ABC q24h had a C_{min} < 0.015 mg/L, vs. 2 out of the 5 older children (p=0.03).
- This finding seems of little clinical relevance due to the long intracellular half-life of ABC's active moiety. For ABC q12h, no such difference seemed present: 1/9 younger children versus 1/5 older children had a C_{min} < 0.015 mg/L (p=0.60).

Safety

- At week 12 after changing to the q24h regimen, no child had discontinued treatment due to adverse events (AEs).
- One case of grade 3 neutropenia occurred at week 12, which resolved at week 24. This AE was considered possibly drug related
- In none of the patients, changes in clinical chemistry and haematology laboratory measurements were observed after changing 3TC and/or ABC from q12h to q24h.

Virologic efficacy (week 12)

- 12 weeks after changing to the q24h regimen, HIV-1 RNA load was <100 copies/mL in 17/20 children (85%), while in 3/20 children, HIV-1 RNA loads were 160, 1600 and 3900 copies/mL, respectively.
- Of these 3 children, 2 had already an HIV-1 RNA load >100 copies/mL at baseline (in the 2 other subjects with an HIV-1 RNA load >100 copies/mL at baseline, viral load had become undetectable at the q24h regimen).
- In the 3rd child with HIV-1 RNA load > 100 copies/mL, viral load increase was caused by a major compliance problem.

| Pharmacokinetic parameter | ABC 8 mg/kg q12h | | | ABC 16 mg/kg q24h | | |
|------------------------------|--------------------------------------|---------------------------------------|---------|--------------------------------------|---------------------------------------|---------|
| | Children ≥ 2 -6 years old (N=9) | Children >6 - <13 years old (N=5) | P-value | Children ≥ 2 -6 years old (N=9) | Children >6 - <13 years old (N=5) | P-value |
| AUC ₀₋₂₄ (mg/L*h) | 9.27 (7.06-12.18) | 11.17 (8.76-14.24) | 0.408 | 13.55 (11.19-16.42) | 13.06 (10.91-15.63) | 0.812 |
| C _{max} (mg/L) | 1.94 (1.50-2.51) | 2.54 (2.00-3.22) | 0.215 | 5.07 (3.92-6.56) | 4.36 (3.39-5.60) | 0.478 |
| C _{min} (mg/L) | 0.027 (<0.015-0.040) | 0.022 (<0.015-0.070) | N.A.* | <0.015 (<0.015-0.015) | 0.016 (<0.015-0.046) | N.A.* |
| (median (range)) | | | | | | |
| Cl/F*kg (L/h*kg) | 1.80 (1.37-2.36) | 1.26 (0.96-1.64) | 0.130 | 1.21 (1.00-1.47) | 1.08 (0.81-1.44) | 0.509 |

*: not available

Conclusions

- These PK data, in addition to good 12-week efficacy, and safety suggest feasibility of q24h use of 3TC and ABC in HIV-1 infected children ≥ 2 - <13 years old with suppressed viral load.
- Therapeutic equivalence of q24h regimens of 3TC and ABC should be further evaluated in a comparative clinical trial.
- The tendency for lower plasma levels of 3TC in younger children poses the question, if higher doses of 3TC should be applied in younger children
- Data on intracellular PK may contribute to the evaluation of the clinical relevance of this finding.

Contact

David Burger, PharmD, PhD
Dept of Clinical Pharmacy
539 UMC St Radboud
P.O. Box 9101
6500 HB Nijmegen
The Netherlands
Phone +31. 24. 3616405
Fax +31. 24. 3540331
dburger@akf.umcn.nl